THE EFFECT OF SUBSTITUENTS IN THE TSCHITSCHIBABIN SYNTHESIS OF PYRIDINES

BY

RAYMOND PETER SEVEN

A.B., Calvin College, 1943
M.S., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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Introduction

Since late in the nineteenth century, considerable study has been made of the reaction of carbonyl compounds with ammonia to obtain cyclic bases, principally substituted pyridines. By far the greatest part of the work on this reaction has been carried out by Tschitschibabin[1] and his name has been rather generally applied to identify this method of pyridine synthesis.

Until recently the reaction has not been of much practical importance, in fact, Sidgwick[2] in his classical "Organic Chemistry of Nitrogen" has stated that "these methods of preparing pyridines are of little synthetical value, chiefly owing to the fact that a mixture of pyridine bases is generally obtained."

The purpose of this investigation has been to study the scope of the method as a practical means of obtaining certain substituted pyridines and to determine the relation of the carbonyl starting compound to the yield and structure of the resulting pyridine derivatives.

The reactions were usually carried out by heating the carbonyl component with ten times the theoretical amount of aqueous ammonia in a steel, high-pressure autoclave. A small amount of ammonium acetate was used as catalyst. The reaction conditions were in most cases 250° for three hours.

Discussion

A study of the literature and of the results of this investi-

gation indicate that four general types of pyridine-forming condensations can occur under the conditions of this reaction. The first two types involve the condensation of two molecules of an α,β-unsaturated carbonyl compound and ammonia, with loss of water. The products of these two reactions differ because of the difference in relative orientation of the reacting molecules. As an example crotonaldehyde can react with ammonia to give either 2-methyl-5-ethylpyridine or 3-methyl-4-ethylpyridine. In this investigation, however, no products of the latter type were encountered even though this type of reaction is known to take place in vapor phase.

The other two types of reaction involve the condensation of ammonia with one molecule of α,β-unsaturated carbonyl compound and one molecule of methyl (or methylene) ketone with elimination of hydrogen as well as water. These two reactions also differ only by the orientation of the two carbonyl groups with respect to the ammonia molecule.

Comparatively good yields (up to 50 per cent) of a single pyridine were obtained when aryl substituted starting materials were used, e.g. substituted chalcones with acetophenone. Because these reactions draw their starting material from an equilibruim mixture of the aldol and Michael condensation products, the pyridines are formed regardless of whether the α,β-unsaturated carbonyl compound is used, the mixture of aldehyde and methyl ketone which go to make it up, or even the 1,5-diketone from one molecule of the aldehyde and two of the methyl ketone. The best yields were obtained, however, when the corresponding 1,5-diketones (Michael condensation products) were used as starting materials, thus indicating that this compound may well be the intermediate in the reaction. An example is given in the following table:

Starting Materials	Yield Of Triaryl Pyridine		
	Grams Theor.	Grams Obtained	Per Cent
p-Chlorobenzaldehyde, Acetophenone	25.6	4.5	17.6
p-Chlorobenzalacetophenone, Acetophenone	25.6	8.3	32.4
p-Chlorobenzaldiacetophenone	25.6	12.91	50.5

The products of the three reactions listed in the table were shown to be identical by mixed melting point determinations.

As mentioned above, these reactions can occur to give two types of products depending on the orientation of the two carbonyl groups and the α,β-unsaturation with respect to the ammonia molecule. In the example cited above, the product might be 4-*p*-chlorophenyl-2,6-diphenylpyridine or 2-*p*-chlorophenyl-4,6-diphenylpyridine although the high yield from the 1,5-diketone indicates that it is probably the former. Further proof was afforded by the unequivocal synthesis of 4-*p*-chlorophenyl-2,6-diphenylpyridine by the reaction of *p*-chlorobenzaldiacetophenone with hydroxylamine hydrochloride. This product was shown to be identical with the product formed from the condensation of the 1,5-diketone with ammonia, thus establishing that when the substituents vary, the ammonia condensation reaction does occur chiefly to give the symmetrically substituted pyridine. This contention was also upheld by similar evidence with the anisyl group substituted for the *p*-chlorophenyl ring.

Two attempts were made to extend the reaction by using an α,β-unsaturated ketone with a methyl ketone different from the one used to make the unsaturated ketone. In reactions of benzalacetophenone with acetone and of benzalacetone with acetophenone the only product isolated in either case was benzylacetophenone. The latter case illustrates the reversal

of the aldol condensation followed by a different recombination and then hydrogenation of the double bond by hydrogen formed in the pyridine-forming condensation. The results of both these reactions indicate that in order to obtain a yield of a single pyridine, starting materials must be chosen so that only one methyl ketone component will exist in the aldol condensation equilibrium mixture.

The effect of ethoxyl substituents on the carbonyl component was also investigated. The high yields of aldehyde-collidine (2-methyl-5-ethylpyridine) obtainable from the reaction of paraldehyde with ammonia[3] suggested that it might be possible to "protect" the carbonyl component of the reaction by acetalization with ethyl alcohol. This "protection" was most striking when use was made of the 1,1,3-triethoxy alkanes formed from the α,β-unsaturated carbonyl compounds, whereas mere acetalization had little effect. The use of acetal in the formation of aldehyde-collidine gave yields comparable to those in which paraldehyde was used. A good yield of 2,3,4-collidine was obtained when β-ethoxyethyl methyl ketone was used as starting material. This type of ethanol addition product may probably be useful in connection with other α,β-unsaturated carbonyl compounds.

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VITA

The author was born in Grand Rapids, Michigan, on December 5, 1921. He attended the Christian Schools of that city and was graduated from Grand Rapids Christian High School in June, 1939. In the fall of that year he entered Calvin College in Grand Rapids, Michigan. After three years of study at that institution, followed by one year of a chemical engineering curriculum at the University of Michigan, he was graduated from Calvin College in June, 1943, with the degree of Bachelor of Arts. Having enlisted in the Army in October, 1942, he was called to active duty in June, 1943. After basic military training and study on the Army Specialized Training Program he was assigned in September, 1944, to the Manhattan Project at Oak Ridge, Tennessee, as a chemical engineer. He was discharged from the Army in March, 1946, at which time he entered the Graduate College of the University of Illinois. He held a part-time teaching assistantship from September, 1946, to September, 1947, and University Fellowships from September, 1947, to February, 1949. In February, 1947, he received his Master of Science degree from the University of Illinois.

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